Screening for transcatheter mitral valve replacement: a decision tree algorithm

Sebastian Ludwig[1], MD; Nicole Ruebsamen[1,2], PhD; Florian Deuschl[1], MD; Niklas Schofer[1], MD; Daniel Kalbacher[1], MD; Andreas Schaefer[3], MD; Benedikt Koell[3], MD; Dirk Westermann[1], MD; Hermann Reichenspurner[3], MD, PhD; Stefan Blankenberg[1], MD; Ulrich Schaefer[4], MD; Lenard Conradi[3], MD; Edith Lubos[1]*, MD

1. Department of Cardiology, University Heart and Vascular Center Hamburg, Hamburg, Germany; 2. Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany; 3. Department of Cardiovascular Surgery, University Heart and Vascular Center Hamburg, Hamburg, Germany; 4. Department of Cardiology, Angiology and Intensive Care, Marienkrankenhaus, Hamburg, Germany

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Abstract

Aims: The high frequency of screening failure for anatomical reasons in patients with severe mitral valve regurgitation (MR) is a limiting factor in the screening process for transcatheter mitral valve replacement (TMVR). However, data on optimal patient selection are scarce. The present study aimed to develop a screening algorithm based on TMVR screening data.

Methods and results: A total of 195 screenings for six different TMVR devices were performed in 94 high-risk patients with severe MR. We compared baseline echocardiographic and multislice computed tomography (MSCT) parameters between the subgroups of patients accepted (N=33) and rejected for TMVR (N=61). Reasons for screening failure were assessed, and a decision tree algorithm was statistically derived. Reasons for screening failure were small LV dimensions (30.6%), small (7.5%) or large (22.5%) annular size, potential risk of LVOT obstruction (22.0%) or mitral annulus calcification (15.6%). A four-step decision tree algorithm to assess TMVR eligibility was developed resulting in an AUC of 0.80 (95% CI: 0.71, 0.89, p<0.0001).

Conclusions: This study presents the first screening algorithm to assess anatomical eligibility for TMVR in patients with severe MR, based on simple MSCT criteria. Given the high rate of TMVR screening failure, this algorithm may facilitate the identification of potential TMVR candidates.

*Corresponding author: Department of Cardiology, University Heart and Vascular Center Hamburg, Martinistrasse 52, 20246 Hamburg, Germany. E-mail: e.lubos@uke.de

Abbreviations

ATA   annulus-to-apex
DMR   degenerative mitral valve regurgitation
FMR   functional mitral valve regurgitation
IC   intercommissural
MAC   mitral annulus calcification
MR   mitral valve regurgitation
MSCT   multislice computed tomography
SL   septal-lateral
TMVR   transcatheter mitral valve replacement
TT   intertrigonal

Introduction

Transcatheter mitral valve replacement (TMVR) represents a complementary therapeutic approach for surgical high-risk patients with severe mitral valve regurgitation (MR). This novel therapy promises to reduce MR as durably as surgical valve replacement while reducing the procedural risk with an interventional approach[1]. Given the complex structure of the mitral valve apparatus and possible interactions of an implanted device with anatomic structures, careful patient selection by echocardiography and multislice computed tomography (MSCT) screening is required[2,3]. ECG-gated cardiac MSCT enables comprehensive 3D volumetric assessment by providing an exact characterisation of the anatomy of the subvalvular apparatus and the geometry of the mitral valve[4].

During the screening process, a majority of patients is deemed ineligible for TMVR due to clinical or anatomical reasons, resulting in a high rate of screening failure[5-7]. An evidence-based selection algorithm may facilitate and improve decision making in the screening process for TMVR[1]. This study aimed to create a statistically derived decision tree based on anatomical screening data, enabling simple and reliable identification of potential TMVR candidates.

Methods

STUDY POPULATION

From 2016 to 2019 a total of 94 high-risk patients with severe MR who were considered ineligible for surgery or endovascular edge-to-edge repair underwent screening for TMVR at our centre. Anatomical eligibility was assessed on the basis of MSCT and echocardiographic patient data. Patients were screened for six different dedicated transapical or transseptal TMVR devices. Devices and numbers of screened patients per device are given in **Supplementary Table 1**. Patients not clinically suitable for TMVR were excluded from the study beforehand. All patients provided written informed consent for device screening and data acquisition.

Detailed information on the TMVR screening process is given in **Supplementary Appendix 1**.

ECHOCARDIOGRAPHIC ANALYSES

Transthoracic and transoesophageal echocardiography were performed in every patient for assessment of MR severity and aetiology as well as functional and morphological status. Evaluation of MR was performed according to the 2017 ESC/EACTS guidelines for the management of valvular heart disease[8]. Mean mitral gradient effective regurgitant orifice area (EROA), vena contracta diameter, mitral regurgitation volume and systolic pulmonary artery pressure were documented according to a standardised protocol. Furthermore, left ventricle (LV) characterising parameters were assessed including LV ejection fraction (EF), LV end-diastolic diameter (LVEDD) and volume (LVEDV) as well as LV end-systolic diameter (LVESD) and volume (LVESV).

CARDIAC MSCT ANALYSES

ECG-gated full cardiac cycle MSCT was performed in every patient who underwent the screening process. Subsequently, a dedicated software (3mensio Structural Heart V9.1; Pie Medical Imaging, Maastricht, the Netherlands) was used to assess the mitral valve complex, LV dimensions, LVOT and aortomitral continuity at 30% (end-systole) and 75% (mid-to-end-diastole) of the cardiac cycle, as suggested previously[4]. Mitral valve annulus was sized according to the D-shaped annulus concept that has been described previously[9]. Accordingly, mitral valve annulus perimeter and area were assessed as well as septal-lateral (SL) diameter, intercommissural (IC) diameter and intertrigonal (TT) distance **(Figure 1**, **Figure 2)**[10]. Mean mitral annulus diameter (Dmean) was calculated according to Abdelghani et al: [(IC diameter + SL diameter) / 2][11]. In addition, MSCT analyses comprised LV dimensions (annulus-to-apex [ATA] distance) **(Figure 1A, Figure 2A)**, aortomitral angulation, distances to anterolateral and posteromedial papillary muscles and the extent of mitral annulus calcification (MAC). Native left ventricular outflow tract (LVOT) area was standardly measured at 5 mm below the aortic valve annulus in end-systole.
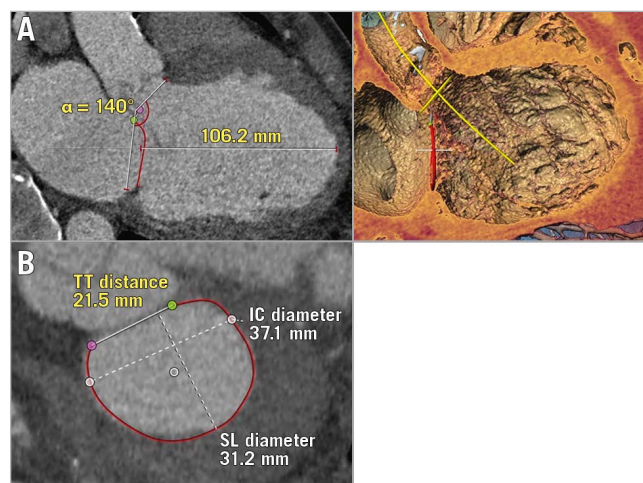

Figure 1. *Favourable TMVR anatomy (example). MSCT reconstruction via 3mensio Structural Heart V9.1. A) End-diastolic 2D (left) and 3D (right) three-chamber view with flat aortomitral angle and large annulus-to-apex (ATA) distance. B) Measurements of D-shaped mitral valve annulus including intertrigonal (TT) distance, intercommissural (IC) diameter and septal-lateral (SL) diameter.*
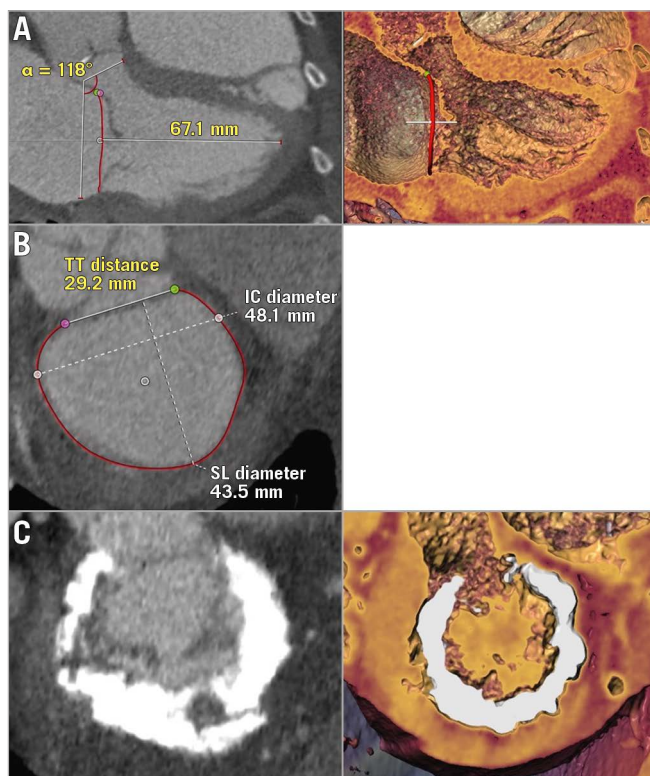
Figure 2. *Unfavourable TMVR anatomies (examples). A) End-diastolic 2D (left) and 3D (right) three-chamber views with acute aortomitral angle, small native LVOT and small ATA distance. B) Measurements of a large mitral valve annulus including TT distance, IC diameter and SL diameter C) Circumferential mitral annulus calcification.*

STATISTICAL ANALYSIS

Patients (N=94) were stratified according to acceptance for a TMVR device (accepted group; n=33, 35.1%) or ultimate rejection for all devices screened for (rejected group; n=61, 64.9%). We considered echocardiography and MSCT variables as potential predictors of an eligible or an ineligible TMVR anatomy. We excluded variables with more than 30% missing values and variables that were used to calculate other variables among the set of potential predictors. Eventually, 15 echocardiography and MSCT variables were left as input for the derivation of the decision tree algorithm **(Supplementary Table 2)**. KNIME version 3.7.2 was used to derive a decision tree with the Gini index as quality measure and pruning based on minimal description length. A detailed description of the statistical derivation process is given in **Supplementary Appendix 2**.

Results

Clinical baseline characteristics of all patients and of the subgroups (accepted and rejected groups) are presented in **Supplementary Table 3**.

ECHOCARDIOGRAPHIC BASELINE CHARACTERISTICS

Echocardiographic parameters at baseline are shown in **Table 1**. The aetiology of MR was functional in 52.1% (n=49), degenerative in 38.3% (n=36) and of mixed aetiology in 9.6% (n=9) in all screened patients. FMR was present more often in patients accepted for TMVR, whereas rejected patients more frequently suffered from DMR than accepted patients. Accordingly, patients in the accepted group had significantly lower baseline EF and

Table 1. Echocardiographic baseline parameters.

Echocardiographic parameters	All patients (n=94)	Accepted group (n=33)	Rejected group (n=61)	*p*-value
MR 3+	16 (17.0)	5 (15.2)	11 (18.0)	0.78
MR 4+	74 (78.7)	28 (84.8)	46 (75.4)	0.43
FMR	49 (52.1)	24 (72.7)	25 (41.0)	0.0047
DMR	36 (38.3)	7 (21.2)	29 (47.5)	0.015
Mixed FMR/DMR	9 (9.6)	2 (6.1)	7 (11.5)	0.49
LVEF, %	47.5 (35.0, 58.1)	37.0 (31.8, 48.2)	55.0 (40.4, 61.6)	<0.001
LVEDD, mm	56.0 (50.0, 64.2)	58.0 (52.0, 65.0)	54.0 (47.2, 63.0)	0.28
LVESD, mm	41.5 (33.8, 53.7)	46.0 (41.9, 58.5)	37.5 (32.7, 42.1)	0.20
LVEDV, ml	127.4 (92.8, 167.3)	135.4 (98.1, 232.0)	120.6 (92.3, 155.2)	0.079
LVESV, ml	65.6 (44.3, 99.7)	89.4 (55.4, 153.0)	56.0 (42.5, 82.0)	0.018
Mean mitral gradient, mmHg	3.0 (2.0, 4.0)	2.0 (2.0, 4.0)	4.0 (2.0, 5.0)	0.019
EROA, cm²	0.3 (0.2, 0.5)	0.3 (0.2, 0.4)	0.3 (0.2, 0.5)	0.30
Vena contracta diameter, mm	8.0 (6.7, 9.3)	8.0 (7.0, 9.0)	8.0 (6.3, 9.7)	1.00
Regurgitation volume, ml	50.7 (33.1, 71.2)	40.9 (29.6, 67.2)	54.5 (39.6, 78.0)	0.18
Systolic pulmonary artery pressure, mmHg	54.0 (47.0, 62.8)	50.0 (47.0, 67.3)	55.0 (45.0, 62.1)	0.95
Moderate TR	33 (35.1)	15 (45.5)	18 (29.5)	0.17
Severe TR	19 (20.2)	8 (24.2)	11 (18.0)	0.59
Moderate AS	9 (9.6)	4 (12.1)	5 (8.2)	0.72
Moderate AR	11 (11.7)	4 (12.1)	7 (11.5)	1.00

AR: aortic regurgitation; AS: aortic stenosis; DMR: degenerative mitral valve regurgitation; EROA: effective regurgitant orifice area; FMR: functional mitral valve regurgitation; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; MR: mitral valve regurgitation; TR: tricuspid regurgitation

larger LVESV. Moderate or severe tricuspid regurgitation (TR) was prevalent in more than half of all screened patients. However, there were no statistically significant differences between accepted and rejected patients regarding concomitant heart valve disease. No other differences were observed regarding all other echocardiographic parameters.

MSCT BASELINE CHARACTERISTICS

MSCT baseline parameters are shown in detail in **Table 2**. LV size was significantly different in MSCT measured by systolic ATA distance. Native LVOT area was larger in the accepted group than in the rejected group and circumferential MAC was more frequent in the rejected group. However, the disparity in MAC between accepted and rejected patients did not reach statistical significance. There were no significant differences between the subgroups for all other MSCT parameters.

SCREENING RESULTS AND REASONS FOR SCREENING FAILURE

From a total of 94 patients screened for different TMVR devices, 33 patients were accepted for TMVR device deployment, whereas 61 patients were ultimately rejected for implantation of each

screened device. The majority of patients underwent screening for more than one TMVR device (n=62, 66.0%), resulting in a total number of 195 device screenings performed. The screening failure rate was 83.1% **(Figure 3)**. **Supplementary Table 4** summarises
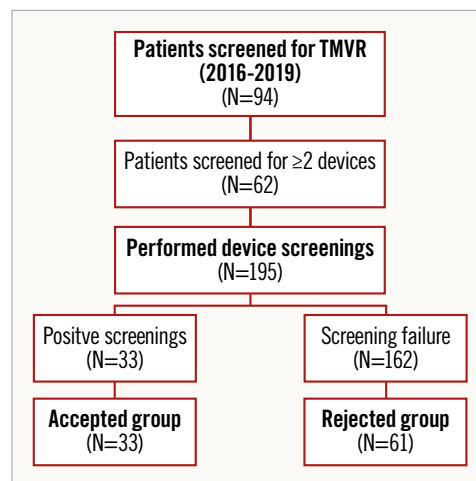

Figure 3. *Flow chart of TMVR screenings performed.*

Table 2. Computed tomography baseline parameters.

Computed tomography parameters	All patients (n=94)	Accepted group (n=33)	Rejected group (n=61)	*p*-value
Mitral annulus area (diastolic), cm^2	11.1 (8.8, 13.3)	11.3 (9.2, 12.2)	10.8 (8.6, 15.0)	0.97
Mitral annulus area (systolic), cm^2	11.6 (9.0, 14.0)	11.4 (9.6, 13.0)	12.1 (8.4, 15.7)	0.71
Mitral annulus perimeter (diastolic), mm	121.2 (109.7, 134.6)	122.4 (111.9, 128.8)	120.3 (108.2, 141.1)	1.00
Mitral annulus perimeter (systolic), mm	125.2 (110.6, 135.7)	124.0 (113.8, 132.0)	126.5 (107.9, 143.0)	0.78
TT distance (diastolic), mm	26.3 (22.1, 30.7)	26.3 (23.1, 31.0)	26.4 (21.8, 30.7)	0.70
TT distance (systolic), mm	26.8 (23.1, 30.2)	26.6 (23.6, 31.2)	27.0 (23.0, 29.5)	0.56
IC diameter (diastolic), mm	35.9 (32.9, 40.9)	35.5 (32.5, 39.5)	36.3 (32.9, 41.7)	0.42
IC diameter (systolic), mm	38.0 (32.8, 41.9)	38.1 (31.8, 39.8)	37.8 (33.2, 42.5)	0.46
SL diameter (diastolic), mm	32.8 (29.0, 37.4)	33.0 (30.3, 35.7)	32.8 (28.2, 38.1)	0.97
SL diameter (systolic), mm	33.3 (29.3, 38.4)	33.0 (31.2, 36.8)	34.3 (28.6, 38.7)	0.55
*Dmean (diastolic), mm	34.6 (31.5, 38.6)	34.0 (32.2, 37.2)	35.4 (30.3, 39.6)	0.71
*Dmean (systolic), mm	35.1 (31.9, 39.6)	35.1 (32.5, 37.8)	35.2 (31.6, 40.6)	0.47
Aortomitral angulation (diastolic), °	131.4 (125.4, 139.2)	134.0 (130.5, 140.2)	130.8 (124.2, 138.3)	0.16
Aortomitral angulation (systolic), °	132.1 (123.3, 136.8)	133.8 (127.6, 137.5)	130.4 (122.5, 136.2)	0.27
Native LVOT area (systolic), cm^2	4.90 (4.07, 5.81)	5.33 (4.48, 6.53)	4.46 (3.72, 5.28)	0.0047
ATA distance (diastolic), mm	91.8 (86.3, 101.8)	99.0 (89.6, 105.2)	91.0 (85.9, 100.7)	0.060
ATA distance (systolic), mm	84.8 (77.6, 95.7)	91.6 (81.5, 99.0)	82.6 (73.9, 90.5)	0.014
Distance to anterolateral PM (diastolic), mm	22.2 (19.0, 24.9)	21.9 (19.2, 27.5)	22.6 (18.6, 24.5)	0.65
Distance to anterolateral PM (systolic), mm	21.7 (18.4, 25.0)	20.6 (17.9, 24.6)	22.0 (18.4, 25.1)	0.65
Distance to posteromedial PM (diastolic), mm	25.7 (21.6, 28.1)	25.6 (23.5, 28.4)	26.2 (20.6, 28.0)	0.43
Distance to posteromedial PM (systolic), mm	25.0 (19.4, 28.6)	25.4 (22.2, 29.3)	24.4 (18.2, 28.5)	0.47
Any MAC	55 (58.5)	16 (48.5)	39 (63.9)	0.19
Circumferential MAC	15 (16.0)	2 (6.1)	13 (21.3)	0.076

*Dmean: (IC diameter/SL diameter)/2. ATA: annulus-to-apex; IC: intercommissural; LVOT: left ventricular outflow tract; MAC: mitral annulus calcification; PM: papillary muscle; SL: septal-lateral; TT: intertrigonal

the screening decisions for all patients and all screened devices, including reasons for screening failure. According to the statements communicated by device manufacturers, five reasons for TMVR screening failure were identified. Spatial restraints of LV dimensions led to the rejection of patients in 30.6%. Mitral annular size was too small in 7.5% and too large in 22.5% of failed screenings. The anticipated risk of LVOT obstruction and MAC were prohibitive conditions in 22.0% and 15.6%, respectively. Maxima and minima of selected baseline MSCT and echocardiography parameters in the accepted group are presented in **Supplementary Table 5**.

Out of 33 patients formally accepted for device deployment, 27 patients eventually underwent TMVR. Three patients died before the planned date of the procedure, two patients withdrew their consent and one patient moved to another city.

DECISION TREE ALGORITHM

A decision tree algorithm was derived taking into account all available baseline MSCT and echocardiographic parameters as well as the results of all TMVR screenings performed (n=195). The best performing decision tree algorithm comprised four essential baseline MSCT parameters leading to either an eligible or an ineligible TMVR anatomy **(Figure 4)**. Of note, baseline echocardiographic parameters were not selected by this algorithm. Stepwise decisions were made on the basis of systolic mitral annulus area (cut-off 8.6 cm^2), systolic Dmean (cut-off 38.3 mm), aortomitral angulation (cut-off 130°) and ATA distance (cut-off 100 mm). The algorithm predicted the correct decision (eligibility or ineligibility
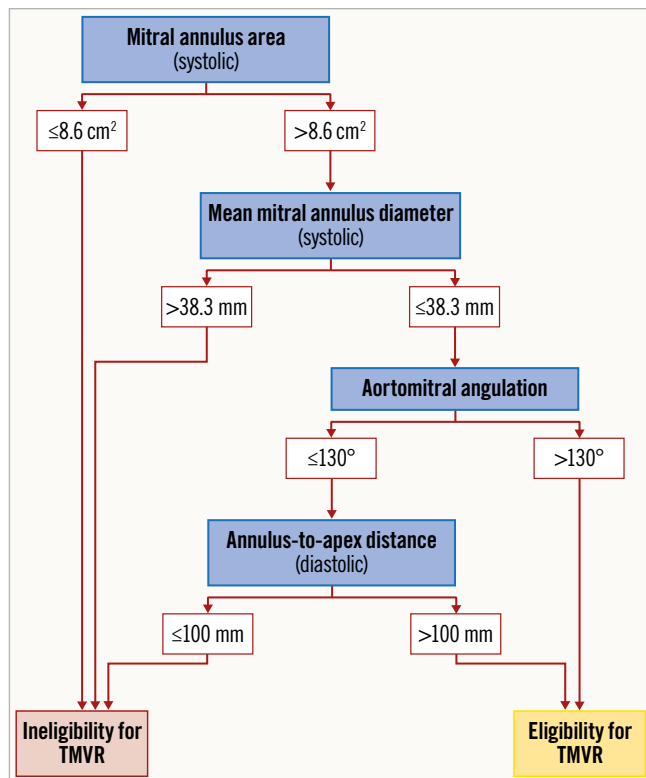
for TMVR) in 81.9% (n=77) of all patients. Nine patients were falsely excluded by the algorithm – two patients for too small an annulus (area ≤8.6 cm^2), six patients for too large an annulus (Dmean >38.3 mm) and one patient for the combination of sharp aortomitral angulation (≤130°) and small LV dimensions (ATA distance ≤100 mm). Conversely, eight patients were incorrectly labelled eligible for TMVR. These discrepancies between observed and predicted decisions resulted in a positive predictive value (PPV) of 75.0% (95% CI: 56.6, 88.5) and a negative predictive value (NPV) of 85.5% (95% CI: 74.2, 93.1). The area under the curve (AUC) for all decisions of the proposed algorithm was 0.80 (95% CI: 0.71, 0.89; p<0.0001) **(Figure 5)**.
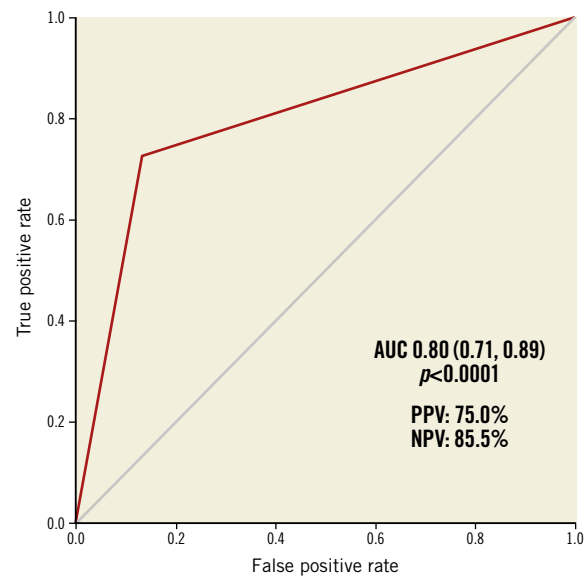

Figure 5. *Statistical performance of the screening algorithm.*

Discussion

This study reports an analysis of the largest single-centre screening experience of patients with severe MR for TMVR to date. Based on a total of 195 device screenings performed in 94 patients across multiple device platforms, we identified common reasons for screening failure and derived a screening algorithm, based solely on MSCT parameters, enabling an accurate identification of MR patients anatomically eligible for TMVR.

Based on the patient population and the device selection available for this study, an "optimal TMVR anatomy" can be defined as follows. First, the mitral annulus size must lie within the size range of the specific device in question. Although the proposed algorithm suggests upper and lower size limits, an up-to-date annular size range should be derived from companies' sizing charts and is highly variable due to the development of new devices. However, our algorithm can help to identify patients with a lower probability of a positive TMVR screening result due to sizing issues.

Figure 4. *Decision tree screening algorithm.*

Second, in order to avoid interference of the valve with LV myocardium, FMR patients seem to represent a preferred target group as LV dimensions are mostly larger in this patient subset compared to DMR patients. This restriction might be softened as new device shapes might focus on reduction of overall device size. In fact, the development of smaller devices will be a key factor for opening TMVR treatment towards a much larger patient population including DMR patients. This is also of particular clinical relevance as a substantial proportion of DMR patients with certain structural leaflet abnormalities (e.g., clefts, very large coaptation defects, Barlow's disease, etc.) are unsuitable for currently available percutaneous mitral valve repair devices and – in cases with high surgical risk – are often left untreated[12].

Third, the risk of LVOT obstruction has to be taken into account. A haemodynamically relevant LVOT obstruction after implantation of the device might have fatal consequences and has to be ruled out prior to TMVR device deployment. A flat aortomitral angle and a large native LVOT play complementary roles in the identification of a favourable anatomy with low risk of LVOT obstruction. A parallel orientation of mitral and aortic annular planes is associated with a low risk, whereas a perpendicular orientation confers a high risk of LVOT obstruction[13]. Regarding individual device geometry, prediction of the minimal cross-sectional area of the neo-LVOT in MSCT should be considered, if virtual valve simulation is accessible[14,15]. A neo-LVOT area of ≤ 2.0 cm^2 is a commonly accepted minimal cut-off for predicted LVOT obstruction[15]. Accordingly, recent studies retrospectively investigating MSCT data prior to TMVR in degenerated mitral bioprostheses, failed mitral annuloplasty rings or extensive MAC by using non-dedicated transcatheter aortic valve implantation devices found that neo-LVOT areas <1.7-1.9 cm^2 were associated with a high risk for haemodynamically relevant LVOT obstruction[16,17]. However, LVOT obstruction is a physiological phenomenon that remains difficult to predict because it depends on multiple, additional factors that have to be considered, e.g., LV size, length of the anterior mitral valve leaflet or diastolic LV function. Moreover, differences in device shape or protrusion of the device into the LV might also have an impact on LVOT obstruction. In this regard, use of TMVR systems with a supra-annular design appears to be an interesting concept that might overcome the limitations of both LV size and LVOT obstruction[18]. However, experience with these devices is limited and further investigation is necessary.

Fourth, although TMVR can be performed in the presence of excessive MAC, it certainly is not a favourable condition as there is a potential risk for incomplete sealing and device unfolding as well as for paravalvular leakage. Initially, severe MAC represented an exclusion criterion for all emerging TMVR studies. Uncertainties about the feasibility of performing TMVR in severe MAC might have contributed to aggressive patient exclusion from device deployment in the early phase of patient recruitment for all TMVR devices. Based on growing clinical experience with TMVR in severe MAC, it is not generally considered a contraindication

for TMVR anymore, and patients with MAC have in fact been treated successfully with TMVR[19]. Accordingly, MAC is not included in the presented algorithm, reflecting a less important role of MAC in screening for TMVR eligibility.

Summarising these criteria, as an example, **Figure 1** demonstrates a favourable TMVR anatomy, as assessed by MSCT, with large LV dimensions, a flat aortomitral angle and a large native LVOT. Conversely, **Figure 2A** and **Figure 2C** show MSCT anatomies of different patients who were rejected because of small LV size and predicted neo-LVOT obstruction **(Figure 2A)**, large mitral annular size **(Figure 2B)** or circumferential MAC **(Figure 2C)**.

The presented decision tree algorithm **(Figure 4)** comprises all relevant parameters that should be considered in the evaluation of a patient's anatomy in the screening for TMVR. Initially, it identifies a lower and an upper limit for eligible annular dimensions, excluding all patients suggestive of very small or very large annuli. Furthermore, it considers the risk of LVOT obstruction by defining a minimum aortomitral angle. The final step of the presented decision tree considers LV size which is represented by diastolic ATA distance. Echocardiographic parameters were statistically outperformed by MSCT parameters. Hence, standard variables such as LVEDD or LVESD were not selected, whereas ATA **(Figure 1A, Figure 2A)**, a less frequently used longitudinal MSCT parameter, plays a decisive role in the algorithm.

Recently, Coisne et al published a study investigating factors associated with TMVR screening failure and success in a series of 40 patients. In line with our results, the authors found a high rate of screening failure and similar reasons for ineligibility. The authors further tested single parameters regarding their ability to predict screening failure. Compared to our results, the assessed cut-offs were considerably higher, reflecting larger annuli in an overall smaller group of investigated patients[20].

Despite the high precision of the presented algorithm, we recommend thorough screening for TMVR eligibility regarding all relevant factors of an optimal TMVR anatomy assessed by a multimodality approach, as described above. Future analyses will have to evaluate whether a screening algorithm predicting anatomical eligibility is also able to predict favourable procedural outcome.

The most relevant value of the proposed algorithm might be the achievement of quicker decision making and the avoidance of vain screening of patients definitely not eligible for any TMVR therapy. Instead, these patients should undergo early evaluation of other therapeutic options (e.g., intensification of medical therapy, edge-to-edge repair with supposedly suboptimal outcome, percutaneous annuloplasty, high-risk surgery).

Limitations

Our study has several inherent limitations. The data presented are the result of a retrospective statistical attempt to reflect the given screening data with the best performing algorithm. The algorithm might need slight adaptation and continuous updating to reflect newly emerging devices or changes in existing device platforms.

Moreover, the applicability of the algorithm might be hampered by the underlying study design which included multiple TMVR devices and, thus, potentially neglected device-related factors for unsuitability. Further, the design as a single-centre experience might have generated bias in screening processes and choice of device. Especially in the early phase of TMVR screening, the decision about the first device screening was arbitrary and based mainly on the availability of devices. Lastly, both pre-screening of patients included in the analysis and an aggressive patient exclusion in the initial phase of patient selection might have biased our results to a certain extent.

Conclusions

This study attempts for the first time to derive an anatomical algorithm for the screening of patients with severe MR for TMVR. The algorithm is designed as a four-step decision tree based on simple MSCT parameters and might help to identify potential TMVR candidates. Validation of the presented algorithm in a multicentre patient cohort is required to prove its universal applicability.

Impact on daily practice

Based on screening data across multiple device platforms, we provide unique information on an optimal TMVR anatomy. In addition, for the first time, we present a TMVR screening algorithm that might notably contribute to an improved identification of possible TMVR candidates and a reduced occurrence of TMVR screening failure.

Acknowledgements

Conflict of interest statement

S. Ludwig reports travel compensation from Edwards Lifesciences, outside the submitted work. F. Deuschl reports personal fees and non-financial support from Neovasc, Edwards Lifesciences, Abbott and Polares Medical, and is currently a full-time employee with Edwards Lifesciences, involved in tricuspid therapies. N. Schofer reports personal fees from Boston Scientific, and travel compensation from Abbott and Edwards Lifesciences, outside the submitted work. D. Kalbacher reports personal fees from Abbott Vascular and Edwards Lifesciences, outside the submitted work. S. Blankenberg reports grants and personal fees from Abbott Diagnostics, Bayer and Thermo Fisher, grants from Siemens and Singulex, and personal fees from Abbott, AstraZeneca, Amgen, Medtronic, Pfizer, Roche, Novartis and Siemens Diagnostics, all outside the submitted work. L. Conradi received lecture fees from and was a proctor as well as an advisory board member of Abbott and Neovasc during the conduct of the study. E. Lubos reports grants and personal fees from Abbott Vascular and personal fees from Edwards Lifesciences, during the conduct of the study, and personal fees from Abiomed, AstraZeneca, Bayer, New Valve Technology and Novartis, outside the submitted work. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Screening process.

Supplementary Appendix 2. Statistical analysis.

Supplementary Table 1. Number of screened patients per device.

Supplementary Table 2. Variables included in the decision tree analysis.

Supplementary Table 3. Baseline characteristics.

Supplementary Table 4. Screening results and reasons for screening failure.

Supplementary Table 5. Maxima and minima of selected baseline MSCT and echocardiography parameters (accepted group).

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Supplementary data

Supplementary Appendix 1. Screening process

Prior to entering the TMVR screening process, all patients were rejected for mitral valve surgery and endovascular edge-to-edge repair. All decisions concerning screening and treatment of patients were made by mutual consent of an interdisciplinary Heart Team, consisting of an interventional cardiologist, a cardiac surgeon and a cardiac anaesthetist. Choices of device differed depending on availability, in-house experience and date, as companies opened screening for different devices at various points in time. Simultaneous screening for different devices was avoided and further screenings were not initiated until definite rejection for the device in question. Reasons for screening failure were obtained from available statements of the device manufacturers.

Supplementary Appendix 2. Statistical analysis

The decision tree was built via recursive binary splitting. For the first node, all 15 variables were considered. For each value s of a variable X, the data set was split into two parts ($X < s$ and $X \geq s$). This was done for all variables. Then the variable and cut point were chosen such that the resulting tree had the lowest Gini index. This was repeated for each new node until splitting of the data set resulted in fewer than two patients per group.

Supplementary Table 1. **Number of screened patients per device.**

Devices	No. of screenings
Tiara	80
Tendyne	56
HighLife	29
CardiAQ	18
Cardiovalve	8
Caisson	4
Total no. of screenings	195

Devices screened for:

Tiara[TM] (Neovasc, Richmond, BC, Canada), Tendyne[TM] (Abbott Vascular, Santa Clara, CA, USA), HighLife[TM] valve (HighLife Medical, Paris, France), CardiAQ[TM] (Edwards Lifesciences, Irvine, CA, USA), Caisson[TM] (LivaNova, Maple Grove, MN, USA), Cardiovalve[TM] (Cardiovalve, Or Yehuda, Israel).

Supplementary Table 2. **Variables included in decision tree analysis.**

Variables
Aortomitral angulation (diastolic), °
Aortomitral angulation (systolic), °
ATA distance (diastolic), mm
ATA distance (systolic), mm
Dmean (diastolic), mm
Dmean (systolic), mm
Circular MAC
LVEDD, mm
LVEDV, ml
LVEF, %
Mitral annulus area (diastolic), cm^2
Mitral annulus area (systolic), cm^2
Systolic native LVOT, cm^2
TT distance (diastolic), mm
TT distance (systolic), mm

ATA: annulus-to-apex; LVEDD: left ventricular end-diastolic diameter; LVEDV: left venricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MAC: mitral annulus calcification; TT: intertrigonal

Supplementary Table 3. **Baseline characteristics.**

	All patients (n=94)	Accepted group (n=33)	Rejected group (n=61)	*p*-value
Age, years	79.0 (75.0, 82.0)	77.0 (73.7, 81.3)	79.5 (76.0, 82.0)	0.30
Male sex	49 (52.1)	20 (60.6)	29 (47.5)	0.28
BMI, kg/m^2	25.6 (23.2, 29.4)	25.5 (22.8, 29.2)	26.4 (23.2, 30.6)	0.60
Risk stratification				
EuroSCORE II, %	5.6 (3.3, 10.0)	6.3 (3.6, 15.8)	4.8 (2.8, 9.0)	0.063
Cardiovascular risk factors				
Smoking history	37 (39.4)	17 (51.1)	20 (32.8)	0.083
Arterial hypertension	71 (75.5)	25 (75.8)	46 (75.4)	1.00
Diabetes	24 (25.5)	7 (21.2)	17 (27.9)	0.62
Cardiac history				
Coronary artery disease	54 (57.4)	19 (57.6)	35 (57.4)	1.00
H/o myocardial infarction	20 (21.3)	11 (33.3)	9 (14.7)	0.062
H/o cardiac surgery	22 (23.4)	12 (36.4)	10 (16.4)	0.041

Heart failure hospitalisation (last year)	82 (87.2)	30 (90.9)	52 (85.2)	0.53
Comorbidities				
Extracardiac arteriopathy	30 (31.9)	7 (21.1)	23 (37.7)	0.11
COPD	15 (16.0)	5 (15.2)	10 (16.4)	1.00
Atrial fibrillation	71 (75.5)	27 (81.8)	44 (72.1)	0.33
Prior stroke	12 (12.8)	4 (12.1)	8 (13.1)	1.00
Previous dialysis	7 (7.4)	2 (6.1)	5 (8.2)	1.00
Clinical presentation				
NYHA Class III	67 (71.3)	25 (75.8)	42 (68.9)	0.63
NYHA Class IV	20 (21.3)	7 (21.2)	13 (21.3)	1.00
Laboratory parameters				
Creatinine, mg/dL	1.3 (1.1, 1.8)	1.6 (1.1, 1.9)	1.3 (1.1, 1.8)	0.37
NT-proBNP, ng/L	4,078.0 (2,060.6, 7,202.1)	4,862.5 (2,369.4, 6,322.7)	3,323.0 (1,860.3, 7,576.3)	0.54

Data presented are the number (percentage) of patients for categorical variables or median values (25th percentile, 75th percentile) for continuous variables.

BMI: body mass index; COPD: chronic obstructive pulmonary disease; H/o: history of; NYHA: New York Heart Association

Supplementary Table 4. Screening results and reasons for screening failure.

Patients	No. of devices screened	Tiara	Tendyne	HighLife	CardiAQ	Cardiovalve	Caisson
Accepted patient 1	1	✓					
Accepted patient 2	1	✓					
Accepted patient 3	1	✓					
Accepted patient 4	1	✓					
Accepted patient 5	1	✓					
Accepted patient 6	1	✓					
Accepted patient 7	1	✓					
Accepted patient 8	1	✓					
Accepted patient 9	1	✓					
Accepted patient 10	1	✓					
Accepted patient 11	1	✓					
Accepted patient 12	2	✓				n/a	
Accepted patient 13	2	✓	n/a				

Accepted patient 14	3	✓		annulus (+)		n/a	
Accepted patient 15	3	✓	n/a	annulus (+)			
Accepted patient 16	1		✓				
Accepted patient 17	1		✓				
Accepted patient 18	2	annulus (+)	✓				
Accepted patient 19	2	small LV, MAC	✓				
Accepted patient 20	2	small LV, LVOTO	✓				
Accepted patient 21	2	annulus (+)	✓				
Accepted patient 22	2	small LV, LVOTO	✓				
Accepted patient 23	2		✓	n/a			
Accepted patient 24	2	small LV	✓				
Accepted patient 25	2		✓			MAC	
Accepted patient 26	3	small LV	✓	n/a			
Accepted patient 27	3	small LV, LVOTO, MAC	✓		n/a		
Accepted patient 28	3	annulus (+)	✓			n/a	
Accepted patient 29	4	small LV	✓	n/a	LVOTO		

Accepted patient 30	1			✓			
Accepted patient 31	3	small LV	annulus (+)		✓		
Accepted patient 32	4	small LV, LVOTO	LVOTO	LVOTO, MAC	✓		
Accepted patient 33	4	small LV	LVOTO	n/a	✓		
Rejected patient 1	5	small LV, LVOTO	LVOTO	MAC	n/a	annulus (-), MAC	
Rejected patient 2	4	annulus (+)	annulus (+)	n/a	n/a		
Rejected patient 3	4	small LV	small LV		n/a	MAC	
Rejected patient 4	4	small LV	LVOTO	LVOTO	n/a		
Rejected patient 5	4	small LV, MAC	MAC	MAC	n/a		
Rejected patient 6	4	small LV, MAC	annulus (-)	n/a	n/a		
Rejected patient 7	4	small LV	LVOTO	annulus (-), small LV	n/a		
Rejected patient 8	3	small LV	n/a	annulus (-), small LV			
Rejected patient 9	3	annulus (+)	annulus (+)			annulus (+)	
Rejected patient 10	3		annulus (+)		annulus (+)	annulus (+)	
Rejected patient 11	3	small LV	n/a	n/a			
Rejected patient 12	3		n/a	n/a			n/a

Rejected patient 13	3	small LV, LVOTO	MAC	MAC			
Rejected patient 14	3	MAC	MAC	n/a			
Rejected patient 15	3	annulus (+)	annulus (-)		n/a		
Rejected patient 16	3	small LV, LVOTO, MAC	LVOTO	n/a			
Rejected patient 17	3	small LV, LVOTO, MAC	annulus (-)	n/a			
Rejected patient 18	3		n/a	n/a			annulus (+)
Rejected patient 19	3	small LV	n/a	LVOTO			
Rejected patient 20	2	annulus (+), small LV, LVOTO, MAC		annulus (+), small LV, LVOTO, MAC			
Rejected patient 21	2	small LV		n/a			
Rejected patient 22	2	annulus (+), small LV, LVOTO	LVOTO				
Rejected patient 23	2	small LV			annulus (+)		
Rejected patient 24	2	annulus (+)			annulus (+)		
Rejected patient 25	2	n/a		n/a			
Rejected patient 26	2		n/a	annulus (+)			
Rejected patient 27	2	small LV	LVOTO				

Rejected patient 28	2	small LV, LVOTO			n/a		
Rejected patient 29	2	small LV, LVOTO	small LV				
Rejected patient 30	2	annulus (+), small LV	LVOTO				
Rejected patient 31	2	small LV, LVOTO	annulus (-)				
Rejected patient 32	2	small LV	LVOTO				
Rejected patient 33	2	annulus (-), small LV, MAC	annulus (-)				
Rejected patient 34	2	small LV	n/a				
Rejected patient 35	2	annulus (+)					annulus (+)
Rejected patient 36	2	annulus (+)	annulus (+)				
Rejected patient 37	2	annulus (-), MAC	MAC				
Rejected patient 38	2	annulus (-), small LV, LVOTO, MAC	LVOTO				
Rejected patient 39	2	small LV		n/a			
Rejected patient 40	2	small LV, LVOTO	LVOTO				
Rejected patient 41	2	MAC	n/a				
Rejected patient 42	2		n/a	annulus (+)			

Rejected patient 43	2	annulus (+), small LV	annulus (+)				
Rejected patient 44	1	small LV, LVOTO					
Rejected patient 45	1	annulus (+), small LV, MAC					
Rejected patient 46	1	small LV					
Rejected patient 47	1	n/a					
Rejected patient 48	1		n/a				
Rejected patient 49	1						annulus (+)
Rejected patient 50	1	annulus (+)					
Rejected patient 51	1	small LV, LVOTO					
Rejected patient 52	1				annulus (+)		
Rejected patient 53	1	small LV					
Rejected patient 54	1	n/a					
Rejected patient 55	1	small LV, LVOTO					
Rejected patient 56	1		annulus (-)				
Rejected patient 57	1	annulus (+)					
Rejected patient 58	1	n/a					

Rejected patient 59	1	n/a					
Rejected patient 60	1	n/a					
Rejected patient 61	1	n/a					

Differences in numbers of screened devices depended on available devices at the respective point in time.

annulus (+): annulus too large; annulus (-): annulus too small.

LV: left ventricle; LVOTO: left ventricular outflow tract obstruction; MAC: mitral annulus calcification; n/a: not accepted (the patient was rejected for the respective device for anatomical reasons, but no information about the exact reason for screening failure was provided by the company).

✓: The patient was accepted for the respective device.

Supplementary Table 5. **Maxima and minima of selected baseline MSCT and echocardiography parameters (accepted group).**

	Accepted group (n=33)
Echocardiographic parameters	
LVEDD, mm	36.0—74.0
LVESD, mm	30.0—59.0
LVEDV, ml	68.2—338.4
LVESV, ml	29.0—241.0
Computed tomography parameters	
Mitral annulus area (diastolic), cm^2	8.0—16.0
Mitral annulus area (systolic), cm^2	8.1—16.6
Mitral annulus perimeter (diastolic), mm	106.1—146.7
Mitral annulus perimeter (systolic), mm	106.3—146.0
*Dmean (diastolic), mm	27.2—43.4
*Dmean (systolic), mm	28.5—43.2
Aortomitral angulation (diastolic), °	116.0—177.7
Aortomitral angulation (systolic), °	113.3—147.3
Native LVOT area (systolic), cm^2	3.62—8.72
ATA distance (diastolic), mm	75.1—118.7
ATA distance (systolic), mm	52.1—112.6

*Dmean: (IC diameter/SL diameter)/2

ATA: annulus-to-apex; LVEDD: left ventricular end-diastolic diameter; LVEDV: left venricular end-diastolic volume; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; LVOT: left ventricular outflow tract; MSCT: multislice computed tomography